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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Guillermo G. Mor, et al
Serial No.:	10/779,360
Confirmation No.:	7903
Filed:	February 13, 2004
For:	IN VITRO TEST TO DETECT RISK OF PREECLAMPSIA
Examiner:	B. Shen
Art Unit:	1657

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to MAIL STOP AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the 20th day of ~~November~~ December, 2007. 12/20/07

Melissa L. B. Lyons

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

1. I, Guillermo Mor, M.D., Ph.D., am a physician with extensive training and experience in the fields of reproductive immunology and obstetrics and gynecology, including fundamental analysis and therapeutic applications; immunological mechanisms active in pregnancy; and reproductive disorders including preeclampsia and cancer. A copy of my Curriculum Vitae is attached as Exhibit A.

2. I am head of the Reproductive Immunology Unit in the Department of Obstetrics, Gynecology, and Reproductive Sciences at Yale Medical School, New Haven, Connecticut. I receive salary from the Yale Medical School. My research funding is derived from U.S. government grants and industry contracts.

3. I have read the above-identified patent application, the pending claims, and the Office Action dated July 20, 2007.

4. As indicated at pages 2 – 4 of the Office Action, the Examiner rejected claims 2, 3, 25, and 26 as obvious over Neale, et al. [Meeting abstract Am J. Obs & Gyn 2001;185(6-s1) page S83, 22nd Annual Meeting of the Society for Maternal-Fetal Medicine]. The Examiner concludes (page 3) that Neale et al renders obvious Applicant's claimed invention because Neale et al. "suggest that their assay may be the first steps in the development of a screen test for patients at high risk for preeclampsia." Further, the Examiner states it "would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Neale by testing pregnant woman (sic) to see if they are at risk of developing preeclampsia because the method compares trophoblast sensitivity to Fas mediated apoptosis between serum from normal pregnancies and preeclampsia" and "one would have been motivated to make the modification because Neale suggest in the title that trophoblast viability can be used as a predictor of preeclampsia." The Examiner concludes that the "invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary."

5. I am providing information in support of the conclusion that the claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made based on the disclosure of the Neale et al. abstract, of which I am an author. I was well aware of the state of the art in preeclampsia diagnostics at the time of publication of the abstract and at the priority date of the above-referenced application. The knowledge in the art at the time of filing was such that one of ordinary skill would not have been motivated to use the claimed screening method to test non-preeclamptic pregnant women as early as the first trimester of pregnancy to predict whether or not the women would develop preeclampsia later in pregnancy. In addition,

due to the level of understanding of markers for preeclampsia at the time of filing, there would have been no reasonable expectation of success in adapting the teaching of the Neale et al. abstract to make an assay for use as early as the first trimester of pregnancy to predict of risk of preeclampsia.

The ability to use an assay to diagnose preeclampsia in a woman is very different than the ability to use the assay to predict as early as the first trimester of pregnancy whether or not a woman is at risk for eventually developing the disorder. There is no basis to conclude that one of ordinary skill in the art at the time of the publication of the Neale et al. abstract would have predicted that a serum component present in women in the third trimester of pregnancy and known to have preeclampsia would also be present as early as the first trimester of pregnancy and could be used as a marker to predict risk of later preeclampsia. At the time we developed an assay that could be used to indicate the risk of later preeclampsia as early as the first trimester of pregnancy, it was totally unexpected that the assay could be effective at such an early stage of pregnancy, well in advance of any clinical indication of the disorder.

6. Further evidence of the unexpected nature of the assay to predict the later development of preeclampsia can be seen in the responses of scientific journal editors to manuscripts I submitted describing my discovery of an assay that could be utilized as early as the first trimester of pregnancy to predict a woman's risk of developing preeclampsia. The uniformly negative responses received from well-respected journals, including *Human Reproduction, Journal of Immunology*, and *Journal of Obstetrics and Gynecology,* support a conclusion that the claimed invention was not obvious at the time of filing. Prior to and coincident to the time of filing, I submitted to various journals manuscripts describing a trophoblast assay as a predictor of risk of later development of preeclampsia. The editors of each journal expressed disbelief that preeclampsia would initiate detectable changes several months in advance of the onset of clinical symptoms. The editors indicated their belief that preeclampsia had an acute onset and that risk of preeclampsia was not an identifiable phenomena at such an early time in pregnancy. The

responses of the editors to my method demonstrates that at the time of filing even the suggestion that the risk of developing preeclampsia could be detected months in advance of the onset of preeclamptic clinical symptoms, was not accepted by those knowledgeable in the art.

7. At the time of filing, it was well known to those in the field of diagnostics that in many instances, a marker that is characteristic of a disorder is not useful for predicting risk of developing the same disorder. For example, various markers for preeclampsia had been identified in serum of women known to be preeclamptic. However, none of these markers are useful as early as the first trimester of pregnancy to predict the risk of development of preeclampsia. Examples of markers for preeclampsia include VEGF, TGFβ, and endoglin, each of which may be useful for detecting existing preeclampsia in a pregnancy and for predicting preeclampsia shortly before clinical onset of the disorder. However, none of these markers is predictive of risk of preeclampsia when assayed as early as the first trimester of pregnancy. VEGF and TGFβ have been shown to be elevated in preeclampsia, but their levels only increase during the mid-second to third trimester of pregnancy. Similarly, Endoglin has been recognized as a marker for diagnosis of preeclampsia, but its level only increases after 17 to 20 weeks of pregnancy – well beyond the first trimester.

Additional compounds that are elevated in preeclampsia are not suitable as predictive markers because they are only elevated once clinical preeclampsia is present. An article by Polliotti, B. M. et al., in *Obstetrics & Gynecology* 2003 Vol. 101(6):1266-1274, (copy enclosed as Exhibit B) describes a study in which components in serum from women diagnosed in the third trimester with preeclampsia were assessed in serum that had been obtained from the same women during the second trimester of their pregnancies, which was prior to the onset of clinical symptoms of preeclampsia. Some of the components, such as circulating vascular endothelial growth factor and placental growth factor were identified as useful for assessing risk of preeclampsia, but their usefulness was limited to the second trimester. Other serum components

including endothelin-1, hCG and granulocyte colony stimulating factor were not useful in predicting development of preeclampsia.

8. In addition to serum components known to be indicative of preeclampsia, at the time of filing numerous serum components were known to be present in women with preeclampsia, but were also known to not be useful for predicting a risk of preeclampsia in a pregnant woman. Examples of such compounds include IL-10, IL-4, activin A, HGC, progesterone, estrogen, among others. These serum components have been identified in serum of preeclamptic patients, but they cannot be used to assess risk of future development of preeclampsia in a pregnant woman. At the time of the publication of the Neale et al. abstract, we had identified a characteristic of serum of preeclamptic women that was associated with the existence of the preeclampsia. The identification of such a serum characteristic in preeclampsia does not suggest that the characteristic is in any way predictive of risk of later development of preeclampsia in non-preeclamptic women.

9. The existence of a number of markers for preeclampsia that are not useful to predict *risk* of preeclampsia, and the widely held belief in the art that the first trimester was too far removed from the clinical onset of preeclampsia to permit prediction of risk of development of preeclampsia, support a conclusion that one of ordinary skill in the art would have no reasonable expectation of success in modifying the diagnostic assay disclosed in Neale et al. and would have had no motivation to make the predictive assay of the invention. From the state of the diagnostic arts at the time of filing it is reasonable to conclude that serum components identified as present in preeclamptic women would not have been expected to be useful as predictors of risk of preeclampsia as early as the first trimester of pregnancy. Therefore, the invention as claimed would not have been obvious based on the Neale et al. abstract.

10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above application and any patent or application related thereto.

Guillermo Mor, M.D., Ph.D.

December 19, 2007
Date

Exh. 10 A

Gil G. Mor, M.D., Ph.D.

Associate Professor, Yale University School of Medicine
Director Reproductive Immunology Unit
Director, Translational Research in Gynecologic Oncology: Discovery To Cure: Ovarian Cancer Detection and Treatment Program
Dept of Obstetrics, Gynecology & Reproductive Sciences
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Research

Major research interest

Regulation of apoptosis in normal tissue remodeling and cancer of the female reproductive tract

A thin line separates normal from neoplastic development. A delicate balance between cell growth and cell apoptosis maintains this homeostatic state. Once that line is breached the same genes protecting the organism from cancer may become involved in its genesis. The genes encoding Fas and FasL, which normally regulate homeostasis yet have the potential to foster malignant growth, exemplify this tenuous balance. The main objective of our studies is to further understand the function and regulation of the genes involved in tissue homeostasis and tumor suppression. We give especial relevance to the role of immune cells as key regulators of tissue homeostasis.

Our studies will provide valuable information related to the biology and development of the normal reproductive tissues. It is important to remember that only with a solid foundation of the normal physiology can we take the first steps towards understanding cancer, allowing us to develop new strategies for its treatment and prevention.

Research interests

Sex Hormones and the Immune system

- Changes in the immune response during menopause

- The effect of Hormone Replacement Therapy in the immune system
- Characterization of estrogen receptors (ER) in cells of the immune system
- The role of estrogen receptors α and β in cell proliferation and apoptosis

We have developed an in vitro system to test the effect SERMs on cell growth and apoptosis according to the ER subtype.

Immunology of Gynecologic tumors

- Apoptosis and cancer
- Hormonal and growth factor regulation of the Fas/FasL system in gynecologic tumors
- Markers for early detection and tumor response in ovarian cancer
- Inflammation and tumor formation

Immunology of Implantation

- Cellular mechanisms mediating the interaction between trophoblast and immune cells
- The role of macrophages in pregnancy
- Innate immunity and pregnancy: expression and role of Toll-like receptors (TLR) in trophoblast cells

"Apoptosis and Cancer: basic mechanisms and new therapeutic opportunities"

Epithelial ovarian cancer (EOC) is the fourth leading cause of cancer-related death in women in the United States and the leading cause of gynecologic cancer death. The major limitations in the treatment of ovarian cancer are: i) the lack of an early detection tumor marker, and ii) the resistance to chemotherapeutic agents. This proposal is based on the hypothesis that induction of apoptosis in target cells is a key mechanism of action for most anti-tumor therapies and that defects in apoptosis can lead to chemoresistance. Therefore, we propose that therapeutic modulation of the factor(s) blocking apoptosis may represent a specific approach for cancer therapy. Using an *in vitro* model system, we have identified intracellular factors acting as blockers of apoptosis that confer resistance to conventional chemotherapeutic agents including carboplatin, paclitaxel and taxotere. We also have demonstrated that the isoflavone derivative, Phenoxodiol, effectively removes these blockers of apoptosis, inducing cell death in chemoresistant EOC cells, *in vivo* and *in vitro*. In Phase I and Phase II clinical studies we have shown that Phenoxodiol exhibits little patient cytotoxicity, yet induces cytotoxic effects in chemoresistant EOC cells. It is our hypothesis that Phenoxodiol, by regulating the components of the apoptotic pathway, acts as a chemosensitizer and renders chemoresistant EOC cells chemosensitive. We also hypothesize that specific biochemical products of the apoptotic process may be markers for monitoring early response to therapeutic treatments while the tumor-specific antibodies may be markers for late-stage or durable therapeutic response.

"Ovarian Cancer Translational Research laboratory"

The major limitations in the treatment of ovarian cancer are: i) the lack of an early detection tumor marker, and ii) the resistance to chemotherapeutic agents. Presently there is no commercially available test that is diagnostic for either early or advanced stage epithelial ovarian cancer. The most commonly used test CA125 identifies a group of cell surface glycoproteins which have uncertain biological behavior and very limited clinical utility for the detection of early stage disease (less than 47% accuracy).

Chemotherapy in the treatment of cancer was introduced into the clinical practice more than fifty years ago. Although this form of therapy has been successful for the treatment of some forms of cancer, it has not been the case for the majority of epithelial cancers of the breast, colon, lung and ovary. In addition, the collateral damage to normal cells, systemic toxicity due to lack of specificity, rapid drug metabolism and acquired drug resistance are important clinical problems that have not been solved.

The objective of the translational research program is to approach these two main areas by:
1) Developing new markers for early detection
2) Developing markers that can predict chemoresponse
3) Characterizing new therapeutic strategies for ovarian cancer

Ovarian Cancer Tissue Bank (OCTB)
The Ovarian Cancer Tissue Bank is located at the Department of Obstetrics and Gynecology and contains approximately 400 tissue samples of the primary and metastatic ovarian cancers as well as tissue samples from normal ovaries. In addition, as part of the NCI Ovarian Cancer Detection Program, the facility has in storage ascites and serum samples from patients with ovarian cancer and normal age matched controls.
An important component of the Tissue Bank is its panel of ovarian cancer cells (n=36) isolated from ascites and 10 immortalized normal Ovarian Surface Epithelial cells (OSE). One PhD and two technicians are in charge of the maintenance and organization of the facility. The panel is regularly used for the screening of new compounds that may have cytotoxic effects on ovarian cancer.

"Immunology of Implantation"

Important reproductive events including implantation, trophoblast invasion, placental development and immune protection are regulated by the immune system at the maternal-fetal interface. This maternal-fetal immune interaction is complex and it is difficult to perceive the whole process based on one mechanism of action. Clearly there are multiple mechanisms for the induction of peripheral and local tolerance during pregnancy that prevent fetal rejection while maintaining a strong and active immune surveillance against viral or bacterial infections, which may endanger the successful outcome and the survival of the species. Our studies evaluate the interaction between trophoblast cells and maternal immune cells.

Specifically we study:
1) The role of the Fas/FasL system in immune protection and survival of trophoblast cells
2) The role of innate immune cells, macrophages and dendritic cells, on tissue remodeling and induction of tolerance during implantation
3) The role of trophoblast cells as component of the innate immune system and the recognition of pathogens through the expression of Toll-like receptors
4) Mechanism of action of sex hormones as regulators of immune responses

Reproductive Immunology Tissue Bank (RITB)

In addition the laboratory has a tissue bank consisting on normal and pathologic placenta samples, blood samples from normal pregnancies and complication of pregnancies. The unit has also developed several first trimester trophoblast cell lines, decidual, and endothelial cell lines.

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PERSONAL DATA

Date of birth:	December 23, 1960.
Citizenship:	Israeli, USA.
Languages:	English, Hebrew, and Spanish.
Social Security #:	216-39-5079
Web Page:	http://info.med.yale.edu/obgyn/reproimmuno/

EDUCATION:

1987	**M.D.**, Hebrew University, Medical School, Jerusalem Israel.
1988	**M.Sc.**, Neuroendocrinology, Neurology Department, Hadassah Hospital, Hebrew University, Jerusalem, Israel.
1993	**Ph.D.**, Immunoendocrinology, Hormone Research Department, Weizmann Institute of Science. Rehovot, Israel,

TRAINING

1994-1996	Postdoctoral fellow, Laboratory of Immunobiology, Center for Biologics Evaluation and Research, FDA, National Institutes of Health, Bethesda, MD.
1988-1993	Ph.D. thesis research in the laboratory of Prof. Fortune Kohen, Department of Hormone Research, The Weizmann Institute of Science, Rehovot, Israel.

1991	Fellowship Reproductive Endocrinology, Max-Planck Institut fur Experimentally Endocrinologie. Hanover, Germany.
1990-1993	Clinical training in Reproductive Endocrinology, Department of Obstetrics and Gynecology, Kaplan Hospital, Rehovot, Israel.
1986-1988	M.Sc. thesis research in the laboratory of Prof. Shaul Feldman, Neurology Department, Hadassah Hospital, Hebrew University, Jerusalem, Israel.

ACADEMIC APPOINTMENTS

2008-	Professor Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT
2003-2007	Associate Professor Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT
2004-present	Director, Translational Research in Gynecologic Oncology: *Discovery To Cure*: Ovarian Cancer detection and treatment Program. Department of Obstetrics and Gynecology Yale University/ Yale Cancer Center
1998-2002	Assistant Professor, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT.
1997-present	Adjunct Lecturer, University of New Haven, New Haven, CT.
1997-1998	Associate Research Scientist, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT.

TEACHING EXPERIENCE

2005-	Cell Biology. Graduate level, yearly semester course. Lecture-discussion, 25 students. 3 h/week class time 10 weeks.
2004	Reproductive Immunology Graduate and Medical students. Lectures ; classes time 4 weeks 2h/week

2004 Conference: Topics on cancer therapeutics. Pharmacology Department

2003 Seminar Apoptosis and cancer. Undergraduate students. Four weeks 1 hour/week.

2002-present: Immunology Graduate level, yearly semester course. Lectures, 22-28 students, 3-h/week classes time 10 weeks.

2001-present: Developmental Biology Graduate level, yearly semester course. Lecture-discussion, 15 students. 3 h/week class time 10 weeks.

2001-present: Endocrinology Graduate level, semester course every two years. Lecture-discussion, 15 students. 3 h/week class time 10 weeks.

1999-present: .Undergraduate level, Lecturer on Reproductive Immunology. Course: Human Reproduction.

1997-1998 Instructor. School of Health Sciences, San Francisco's University; Quito, Ecuador. Medical Biology.

Courses and Educational Material

2004- Reproductive Immunology Course. Course Director

2004 Course pack on Reproductive Immunology for Medical Students and Residents. Gil Mor Editor. Landes Bioscience

MENTORSHIP

Donna Neale:	SMFM/AAOGF Scholarship Award 2004
Donna Neale:	NIH, LRP 2002-2004
Shawn Chavez:	PEO Foundation Scholarship Award 2005
David O'Malley:	Research Award from the Gynecologic Cancer Foundation 2004
Michael Kelly:	NIH, LRP 2005
Shawn Chavez:	John Spangler Nicholas Dissertation Award 2006
Aliza Leiser:	Program of Excellence Award Grant, Ovarian Cancer Research Fund 2007
Aliza Leiser::	NIH, LRP 2007-2008

ACADEMIC AWARDS:

Professional Honors or Recognition

A) National

2007: J. Christian Herr Award-Society for Reproductive Immunology

2004: Placental Association of the Americas: Research Award (Mentor)

2002: Society for Maternal-Fetal Medicine: Research Excellence Award (Mentor);

2001: American Society for Reproductive Immunology. New Investigator Award

2000: American Society for Reproductive Immunology Award (Mentor), Annual

2000: Society for Gynecologic Investigation - Blue Ribbon Presentation

1999: American Society for Reproductive Immunology Award (Mentor), Annual

1995: ORISE Fellowship Award

1993: Guerchenson Scholarship Award

B) International

1991: Israel Endocrine Society Award in Basic Endocrine Science

1991: Minerva Training Fellowship Award

2000: Honorary Member, Menopause Society –Chile

2002: Honorary Member, Climacteric Society –Paraguay

2003: Honorary Member, Menopause Society-Argentina

2004: Honorary Member, Argentine Society of Gynecologic Endocrinology

2005: Honorary Member, Obstetric and Gynecologic Society-Ecuador

Professional Service

Peer Review Groups/Grant Study Sections

2007 **Ad Hoc Member:** HED-1 Study Section, NHICD, NIH

2004-present **Grant Reviewer MRC,** London England

2002 **Ad Hoc Member:** Integration Panel Meeting, USAMRDC Ovarian Cancer Research Program

2003 **Ad Hoc Member:** HED-1 Study Section, NHICD, NIH

2003 **Grants Reviewer Wellcome Trust London England**

Professional Organizations

2001-2005 **Elected Councilor:** American Society of Reproductive Immunology

2005-2008 **Elected Secretary of the American Society for Reproductive Immunology**

2003 **Program Chairman** and organizer of the 2003 American Society of Reproductive Immunology Annual Meeting. Yale university, New Haven CT

2004 **Member Editorial Board:** Journal of the Society for Gynecologic Investigation

2005 **Member Editorial Board:** Eureka Bioscience

2005 **Member Editorial Board:** American Journal of Reproductive Immunology

2006 **Member Editorial Board:** Recent Patents in Inflammation & Allergy

2006 **Chief Scientific Officer** Nascent Signs ltd.

Yale University Service –

Medical School Committees

2006 **Translational Research Committee, Yale Cancer Center**

2004 **Yale WRHR Advisory Panel**

2004 **Yale CME Advisory Committee Member,** Yale University School of Medicine

2003 **CME task force.** Yale University School of Medicine

2002 **Organizer and Director:** Discovery To Cure High School Internship

2001-2003 **Web Master.** Department of Obstetrics and Gynecology

MEMBERSHIPS:

- American Association for Cancer Research.
- American Association for the Advancement of Science.
- American Society for Reproductive Immunology.
- Yale Comprehensive Cancer Center.
- Society for Gynecologic Investigation

PROFESSIONAL SERVICES

- **Program Chairman** and organizer of the 2003 American Society of Reproductive Immunology Annual Meeting. Yale university, New Haven CT
- **Ad Hoc Member:** Integration Panel Meeting, USAMRDC Ovarian Cancer Research Program (2002)
- **Ad Hoc Member:** HED-1 Study Section, NHICD, NIH (2003)
- **Ad Hoc Member:** HED-1 Study Section, NHICD, NIH (2007)
- **Secretary of the American Society for Reproductive Immunology** (2005-2008)
- **Councilor:** American Society of Reproductive Immunology (2001-2005)
- **Web Master.** Department of Obstetrics and Gynecology (2001-2003)
- **CME task force.** Yale University School of Medicine (2003)
- **Yale CME Advisory Committee Member,** Yale University School of Medicine (2004)
- **Organizer and Director:** Discovery To Cure High School Internship
- **Yale WRHR Advisory Panel** (2004-present)
- **Member Editorial Board:** Journal of the Society for Gynecologic Investigation (2004-)
- **Member Editorial Board:** Eureka Bioscience (2005-)
- **Member Editorial Board:** American Journal of Reproductive Immunology (2005-)
- **Member Editorial Board:** Recent Patents in Inflammation & Allergy (2006-)
- **CSO Nascent Signs ltd.** (2006-present)

REVIEWER:

Science

Biology of Reproduction.

NeuroImmunoModulation.

European Journal of Obstetrics & Gynecology and Reproductive Biology.

Molecular Human Reproduction.

Journal of Reproductive Immunology

Laboratory Investigation

American Journal of Reproductive Immunology

Obstetrics and Gynecology

Breast Cancer Research and Treatment

Oncogene

Journal of the Society for Gynecologic Investigation

Journal of Immunology

Human Reproduction

Cancer Research

Clinical Cancer Research

Gynecologic Oncology

CLINICAL TRIALS

LABORATORY ORIGINATED CLINICAL TRIALS:

- Phase Ib/II study of Phenoxodiol in patients with recurrent ovarian, fallopian and primary peritoneal cancer that is resistant to second line chemotherapy. 2002-2003
- Phase I study of Neodjuvant use of oral Phenoxodiol in patients with primary diagnosis of squamous adeno-carcinoma of the cervix, vagina and vulva. 2004-
- A non interventional prospective study of the accuracy of the Precision Terapeuthics, INC chemoresponse assay in patients with stage II-IV recurrent epithelial ovarian or primary peritoneal cancer 2004-2005
- Multi-Center, Phase Ib Safety and Preliminary Efficacy Study of Phenoxodiol (Intravenous Dosage Form) as a Chemo-Sensitizing Agent for Cisplatin and Paclitaxel in Recurrent Epithelial Ovarian Cancer 2004-2005
- A Randomized Placebo-Controlled Phase Ib/IIa Safety, Tolerability and Efficacy Study of Oral Phenoxodiol in Combination with Docetaxel versus Docetaxel Alone in Patients with Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer. 2005-

PEER REVIEWED PUBLICATIONS

1. **Mor, G.**, Saphier, D., & Feldman, S. (1986). Inhibition by corticosterone of paraventricular nucleus multiple-unit activity responses to sensory stimuli in freely moving rats. Experimental Neurology, 94(2), 391-399.

2. **Mor, G.**, Saphier, D., & Feldman, S. (1987). Neural pathways that mediate the effects of afferent stimuli on paraventricular nucleus multiunit activity in freely moving rats. Journal of Neuroscience Research, 17(4), 452-458.

3. Saphier, D., Abramsky, O., **Mor, G.**, & Ovadia, H. (1987). Multiunit electrical activity in conscious rats during an immune response. Brain Behavior and Immunity, 1(1), 40-51.

4. Saphier, D., Abramsky, O., **Mor, G.**, & Ovadia, H. (1987). A neurophysiological correlate of an immune response. Annals of the New York Academy of Sciences, 496(354), 354-9.

5. Saphier, D., **Mor, G.**, & Feldman, S. (1988). Neurogenic stimuli alter preoptic area and amygdala unit activity: central effects of olfactory projections on paraventricular nucleus units. Experimental Neurology, 100(1), 71-82.

6. **Mor, G.** (1988). Neural Responses to Neurogenic Stimuli: Effects of Lesions and Glucocorticoids. Thesis. Master of Sciences, The Hebrew University.

7. Ovadia, H., Saphier, D., **Mor, G.**, Maimon, A., & Abramsky, O. (1991). Changes in brain during an immune response. Journal of Neuroimmunology, 17, 253-263.

8. Saphier, D., **Mor, G.**, Ovadia, H., Maimon, A., & Abramsky, O. (1991). Absence of neural responses following suppression of the immune response. International Journal of Neuroscience, 56(1-4), 277-282.

9. Bernard, G., **Mor, G.**, Amir-ZAltsman, Y., & Kohen, F. (1992). Idiometric assay, anti-idiotypes and molecular mimicry. Communication Laboratory and Medicine, 3, 57-62.

10. **Mor, G.**, Amir, Z. Y., Barnard, G., & Kohen, F. (1992). Characterization of an antiidiotypic antibody mimicking the actions of estradiol and its interaction with estrogen receptor. Endocrinology, 130(6), 3633-40.

11. Amir-Zaltsman, Y., **Mor, G.**, Globerson, A., Thole, H., & Kohen, F. (1993). Expression of Estrogen Receptors in Thymocytes. Endocrine, 1, 211-217.

12. Ben-Hur, H., **Mor, G.**, Blickstein, I., Likhman, I., Kohen, F., Dgani, R., Insler, V., Yaffe, P., & Ornoy, A. (1993). Localization of estrogen receptors in vertebrae of human fetuses. Calcified Tissue International, 53, 91-96.

13. Mor, G., Amir-Zaltsman, Y., Barnard, G., Ben-Hur, H., & Kohen, F. (1993). Evidence for the expression of Estrogen Receptors in Monocytes. Endocrine, 1, 387-395.

14. Sömjen, D., **Mor, G.**, Amir, Z. Y., Jaccard, N., Weizman, Y,. Kaye, AM , Kohen, F. (1994). Cell specific stimulation of bone-cells by gonodal-steroids in-vivo and in-vitro. Calcified Tissue International, 54 (4), 342-346.

15. Ben-Hur, H., **Mor, G.**, Blickstein, I., Dgani, R., Insler, V., Amir-Zaltsman, Y., & Kohen, F. (1995). Immunofluorescent assessement of estrogen receptor distribution in normal and pathological human endometrium. Acta Obstetricia et Gynecologica Scandinavica . 74: 97-102.

16. Ben-Hur, H., **Mor, G.**, Insler, V., Blickstein, I., Amir-Zaltsman, Y., Sharp, A., Globerson, A., & Kohen, F. (1995). Menopause is associated with a significant decrease in the expression of estrogen receptors in human peripheral monocytes. American Journal of Reproductive Immunology. 34: 363-369.

17. Sömjen, D., Amir, Z. Y., **Mor, G.** Jaccard, N., Weizman, Y,. Barnard, G., & Kohen, F. (1995). Anti-idiotipic antibody as an estrogen mimetic: Rremoval of the Fc fragment converts agonist to antagonist. Journal of Endocrinology. 145: 409-416.

18. Hagiwara E., **Mor, G.**, Abbasi F., Klinman D. (1995). Phenotype and frequency of cells secreting IL-2, IL-4, IL-6 , IL-10, INFg and TNFa in the peripheral Blood. Cytokines. 7: 815-822.

19. Mor, G., Klinman, D., Shapiro, S., Hagiwara, E., Sedegha, M., Norman, J.A., Hoffman, L.S., Steinberg, A. (1995). Complexity of the cytokine and antibody response elicited by immunizing mice with PyCSP plasmid DNA. Journal of Immunology. 155: 2039-2046.

20. Mor, G., Yamshchikov, G., Sedegah, M., Takeno, M., Wang, R., Hoffman, S., Klinmann, DM. (1996). Induction of Neonatal Tolerance by Plasmide DNA Vaccination. Journal of Clinical Investigation. 98 (12): 2700-2705.

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134. Mor, G. (2008) Inflammation and Pregnancy: The role of TLRs in Trophoblast immune interaction. New York Academy of Science: in press

135. Kelly, M., **Mor, G.,** Goss, G., Kelly, G., Quinn, M., O'Mally, D., Baker, L., McAlpine, J., Azodi, M., Schwartz, P., Rutherford, T. (2008) Phase II evaluation of phenoxodiol in combination with cisplatin or paclitaxel in women with a history of platinum/taxane refractory/resistant epithelial ovarian, fallopian tube or primary peritoneal cancers. Gynecologic Oncology: Submitted

136. Chen, R., Alvero, A., Silasi, D., Kelly, M., Fest, S., Leiser, A., Schwartz, S., Rutherford, P., Visintin, I., **Mor, G.** (2008) Regulation of IKKβ by mir-199 affects NF-κB activity in ovarian cancer cells. Oncogene: Submitted

137. Fraccaroli, L., Alfieri, J., Larocca, L., Calafat, M., Mor, G., Pérez Leirós, C., Ramhorst, R. (2008) A potential tolerogenic immune mechanism by trophoblastic through the activation of chemokine-induced t cell death and t -regulatory cells modulation. Journal of Immunology: Submitted

138. Abrahams, VM., Aldo, P., Murphy, SP., Visintin, I., Romero, R., Sharma, S., Mor, G. (2008) Tlr6 protects trophoblast cells from TLR2/TLR1 mediated apoptosis. Human Reproduction: Submitted

CHAPTER BOOKS

139. **Mor, G.,** and Eliza M., (1998). Autoimmunity and Tolerance. In: *Methods in Molecular Medicine.* Edited by Lowrie, D.B. and Whalen, R. The Human Press Inc.

140. **Mor, G.** and Brown WD (1999) Fas and Fas Ligand mediated immune privileged status of the tumor. In *Cancer Immunotherapy Protocols.* The Human Press Inc

141. **Mor, G.** (2002) Immunology of Reproduction, In: *Infertility and Reproductive Medicine Clinics of North America*

142. Schwartz, PE; Chu, MC; Zheng, W and **Mor, G.** 2002 Endometrial stromal tumors-are they hormonally sensitive? In *Hormone Replacement therapy and Cancer.* Edited by: AR Genazzani The Parthenon Publishing Group

143. **Mor G.** and Abraham V. (2002) Immunology of Implantation. In: *Immunology and Allergy Clinics of North America.*

144. **Mor G** (2002) Sex hormones and the Immune System implication for menopause and autoimmunity. *Women's Health and Menopause Editor: Lobo*, Crosignani, Paoletti and Bruschi Klumer Academic Publisher

145. **Mor G.** (Editor):Introduction to reproductive Immunology, *Immunology of Implantation.* (2004) Landes Bioscience Press ,

146. **Mor, G.**, and Alvero, A. (Editors). (2005) Apoptosis and Cancer. Methods in Molecular Medicine

147. **Mor, G.**, Straszewski-Chavez SL., Abrahams VM. (2004) Macrophage-Trophoblast Interactions . "Placental and Trophoblast Methods and Protocols" for *Methods in Molecular Medicine Series* from Humana Press, Inc. www.eurekah.com

148. Krikun, G., **Mor, G.**, Lockwood, C., (2004), The immortalization of human endometrial cells. Methods in *Molecular Medicine Series* from Humana Press, Inc

149. Abrahams V., **Mor G.** (2004) Tool receptors and pregnancy , *Immunology of Implantation.* (2004) Landes Bioscience Press , www.eurekah.com

150. Chavez, S and **Mor, G.** 2004 The regulation of human trophoblast apoptosis and survival during pregnancy. , *Immunology of Implantation.* (2004) Landes Bioscience Press , www.eurekah.com

151. **Mor, G.**, and Abrahams VM Trophoblast cells as Immune regulators. *Immunology of Implantation.* (2004) Landes Bioscience Press , www.eurekah.com

152. **Mor, G.**, Montagna, M K. and Alvero A B. (2007) Modulation of Apoptosis to Reverse Chemoresistance *Apoptosis and Cancer. Methods in Molecular Medicine Series* from Humana Press, Inc.

153. Dan-Arin Silasi, Ayesha B. Alvero, Jechiel Mor, Rui Chen, Han-Hsuan Fu, Michele K. Montagna and **Gil Mor** (2007) Detection of cancer-related proteins in fresh-frozen ovarian cancer samples using Laser capture microdissection. *Apoptosis and Cancer. Methods in Molecular Medicine Series* from Humana Press, Inc.

154. Ayesha B. Alvero, Michele K. Montagna, and **Gil Mor** (2007) Correlation of caspase activity and *in vitro* chemo-response in epithelial ovarian cancer cell lines. *Apoptosis and Cancer. Methods in Molecular Medicine Series* from Humana Press, In

PAPERS IN PREPARATION

1. Koga, K., and **Mor, G.** (2008) Inflammation and pregnancy
2. Koga, K Aldo P., Abrahams, VM., Mor, G. Viral infection and TLR3 response in pregnancy
3. Joon Song, S. Aschkenazi, T. Rutherford, **Mor G.** (2007) In vitro assay for determination of SERMs-selective activity according to the Estrogen Receptors α and β subtype

BOOKS

IMMUNOLOGY OF IMPLANTATION. Editor: Gil Mor Medical Intelligence Unit Springer, LANDES Bioscience 2006

APOPTOSIS AND CANCER . Editors: Gil Mor and Ayesha Alvero Methods in Molecular Medicine. Human Press. 2007 Vol. 414

PRESENTATIONS AT MEETINGS (up to 2005)

1. **Mor, G.**, Abrahams, V., Straszewski-Chavez, S. The Innate Immune System: Trophoblast Survival and Apoptosis. *American Journal of Reproductive Immunology* 2005; 52 (supplement 1): 15.
2. Abrahams, V.M., Straszewski-Chavez, S.L., Bole-Aldo, P., Romero, R., **Mor, G.** Trophoblast cells regulate an immune response through TLR-4 induced cytokine production. *Journal of the Society for Gynecological Investigation* 2005; 12(2) (supplement 1): 306A.
3. Straszewski-Chavez, S.L., Visitin, I.P., **Mor, G.** XAF1 induces XIAP cleavage and first trimester trophoblast cell apoptosis by acting through the mitochondrial pathway. *American Journal of Reproductive Immunology* 2005; 53(6): 284.
4. Straszewski-Chavez, S.L., Abrahams, V.M., Aldo, P.B., **Mor, G.** Characterization of a novel telomerase-immortalized human first trimester trophoblast cell line. *American Journal of Reproductive Immunology* 2005; 53(6): 285.

5. Abrahams, V.M., Aldo, P.B., Straszewski-Chavez, S.L., Romero, R., **Mor, G.** Toll-like receptor expression and regulation in first trimester trophoblast cells. *American Journal of Reproductive Immunology* 2005; 53(6): 279.
6. Straszewski-Chavez, S.L., Abrahams, V.M., Aldo, P.B., **Mor, G.** The PI3K/Akt pathway inhibits trophoblast apoptosis by regulating $FLIP_S$ and XIAP expression. *Placenta* 2005; 26(8-9): A.60.
7. Straszewski-Chavez, S.L., Abrahams, V.M., Aldo, P.B., **Mor, G.** Isolation and characterization of a novel telomerase-immortalized human first trimester trophoblast cell line. *Placenta* 2005; **26**(8-9): A.62.
8. Abrahams, V.M., Straszewski-Chavez, S.L., Bole-Aldo, P., Romero, R., Mor, G. Trophoblast apoptosis is induced through Toll-like receptor 2, but not Toll-like receptor 4: A novel mechanism for first trimester pregnancy failure. *Journal of the Society for Gynecological Investigation* 2004; 11(2) (supplement 1): 318A.
9. Abrahams, V.M., Kim, Y.M., Straszewski-Chavez, S.L., Romero, R., Mor, G. Efficient clearance of apoptotic cells by macrophages at the maternal-fetal interface is critical for successful pregnancy. *Journal of the Society for Gynecological Investigation* 2004; 11(2) (supplement 1): 281A.
10. Chavez, S., Abrahams, V., Mor, G. XIAP-associated factor 1 (XAF1) is a novel regulator of trophoblast apoptosis. *Placenta* 2004; 25: A14.
11. Alvero, A., Chen, W., Sartorelli, A., Schwartz, P., Rutherford, T., **Mor, G** (2004) Triapine induces apoptosis in chemoresistant ovarian cancer cells. AACR 95th Annual Meeting Orlando FL Abstract # 4897
12. Rutherford, T., O'Malley, D., Makkenchery , Baker, L., Azodi, M., Schwartz, P., **Mor, G** (2004) Phenoxodiol Phase Ib/II Study in Patients with Recurrent Ovarian Cancer that are Resistant to ≥Second Line Chemotherapy. Society for Gynecologic Investigation Houston Texas Abstract # 254
13. **Mor, G.,** Sapi, E., Chen, W., O'Malley, D., Kamsteeg, M., Rutherford T., (2004) Phenoxodiol a Chemosensitizer in Taxotere-resistant Ovarian Cancer Cells. Society for Gynecologic Investigation Houston Texas. Abstract # 984

14. Strasewski-Chavez, S., Abrahams, V., **Mor G.** (2004) TNFα induces trophoblast apoptosis by upregulating XIAP-Associated Factor 1 (XAF-1) Society for Gynecologic Investigation Houston Texas. Abstract # 315

15. Krikun, G., **Mor, G.**, Guller, S., Schatz, F., Sapi, E., Qumsiyeh, M., Lockwood, C. (2004) A novel immortalized endometrial stromal cell line with normal progrestational response Society for Gynecologic Investigation Houston Texas. Abstract # 340

16. Abrahams, VM., Mee-Kim Y., Strasewski-Chavez, S., Romero R., **Mor G.** (2004) Efficient clearance of apoptotic cells by macrophages at the maternal-fetal interface is critical for successful pregnancy. Society for Gynecologic Investigation Houston Texas. Abstract # 616

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18. **Mor, G.** Ying X., Dwipoyono B., Sapi, E., Kamsteeg M., Rutherford T., (2003) Resistance of Ovarian Cancer Cells to Taxotere (Docetaxel) is XIAP Dependent. Society for Gynecologic Investigation Washington DC , Abstract #460)

19. O'Malley, D., Flick, M., Rodov, S. Kacinski, B., Schwartz, P., Rutherford, T., **Mor, G.** (2003) Correlation of in vitro apoptosis and clinical response to chemotherapy in ovarian cancer patients. Society for Gynecologic Investigation Washington DC , Abstract #459)

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22. O'Malley, D., Kamsteeg, M., Chen, W., Schwartz, P., Rutherford, T., **Mor, G.** (2003) Phenoxodiol an d ovarian cancerAnnual Meeting of the American Society for Reproductive Immunology. AJRI 49: Abstract # 372

23. Straszewski, S., Abrahams, V. **Mor, G.** XIAP confers trophoblast cell resistance to Fas-mediated apoptosis (2003) Annual Meeting of the American Society for Reproductive Immunology. AJRI 49: Abstract #326

24. Abrahams V., **Mor, G.** Trophoblast cells secrete an active form of FasL: new insights into implantation (2003). Annual Meeting of the American Society for Reproductive Immunology. AJRI 49: Abstract # 324
25. **Mor, G.**, S. Straszeweski, S.Song, M. Lareef, J. Russo, G. Mor (2002) The regulation of FLIP in Human Breast epithelial cells SGI, Los Angeles Abstract # 4
26. J. Song, E. Sapi, **G. Mor** (2002) Fas Ligand activation by estrogen receptors at the ERE and AP-1 sites SGI, Los Angeles Abstract # 573
27. B. Hanczaruk, E. Sapi, T Rutherfor, **G. Mor** (2002) Regulation of the Fas/FasL system by progesterone in human ovarian cells SGI, Los Angeles Abstract # 850
28. J. Song, M. Cho, S. Chen, **G. Mor**, F Naftolin (2002) The aromatase inhibitor methytestosterone inhibits testosterone-induced breast cancer cell proliferation. SGI, Los Angeles Abstract # 875
29. Donna Neale, Kafui Demasio, Jesica Illuzi, Roberto Romero, ««**GreetingLine**»» (2002) trophoblast viability: can it be used as a predictor of preeclampsia? Society for maternal-Fetal medicine New Orleans, Abstract # 31 (American Journal of obstetrics and Gynecology (185, #6)
30. Joon Song, Sarit Aschkenazi, Thomas Rutherford, Frederick Naftolin, **Gil Mor** (2001) Differential Activation of the Fas Ligand Promoter by SERMs is Dependent on the Estrogen Receptors ERA and ERB Subtype. SGI, Toronto, Abstract t# [811]
31. Joon Song, Frederick Naftolin, Sarit Aschkenazi, Thomas Rutherford, **Gil Mor** (2001) Effect of Estrogen on Fas Ligand Promoter Activity. SGI, Toronto, Abstract t# [816]
32. Steven F Palter, Ali Rustu Ergur, Umit Kayisli, Chunghuan Lin, **Gil Mor** (2001) Time-Course of Human Xenograft Folliculogenesis. SGI, Toronto, Abstract t# [763]
33. Sarit Aschkenazi, Thomas Rutherford, Joon Song, Chunghyun Lim, **Gil Mor** (2001) Thalidomide Induces Fas-Mediated Apoptosis in Epithelial Ovarian Cancer. SGI, Toronto, Abstract t# [72]
34. Joon Song, Sarit Aschkenazi, Frederick Naftolin, **Gil Mor** (2001) Sex Hormones, Apoptosis and the Fas/Fas Ligand System in Normal Endometrial Tissue Remodeling. SGI, Toronto, Abstract t# [438]

35. Ali Rustu Ergur, Umit Kayisli, Ernest Amama, **Gil Mor,** Steven F Palter (2001) Effects of Host Sex on Human Ovarian Xenograft Folliculogenesis and Apoptosis in Immunodeficient Mice. SGI, Toronto, Abstract t# [41]
36. Juan A Garcia-Velasco, Carlos SimÓn, **Gil Mor**, Aydin Aric (2001) Soluble Fas Ligand Is Elevated in Peritoneal Fluid and Serum Of Women with Endometriosis. SGI, Toronto, Abstract t# [383]
37. Sarit Aschkenazi, Thomas Rutherford, Eva Sapi, Joon Song, **Gil Mor** (2001) Cytotoxicity to Taxol in Epithelial Ovarian Cancer Cells Is Mediated by the Fas/Fas Ligand System: In Vitro Assessment of Drug Sensitivity. SGI, Toronto, Abstract t# [277]
38. Ivaldo Silva, **Gil Mor**, Frederick Naftolin (2001) Anti-Inflammatory Effect of Estrogen on Microglia Activation through Down Regulation of CD40 Pathway. SGI, Toronto, Abstract t# [250]
39. Sarit Aschkenazi, **Gil Mor** (2001) TH-1 and TH-2 Type Cytokines Regulates Fas-Mediated Apoptosis in First TrimesterTrophoblast Cells: Role of the Fas/Fas Ligand System in Implantation. SGI, Toronto, Abstract t# [226]
40. Joon Song, Sarit Aschkenazi, Frederick Naftolin, **Gil Mor** (2001) Sex hormones, apoptosis and the fas/fas ligand system in normal endometrial tissue remodeling. SGI, Toronto SGI, Toronto, Abstract t# 438
41. Redlinger R., Poggio, K. Muñoz, A. **Mor, G.** (2000) The role of the Fas/FasL system in the estrogen-induced thymic alteration. . American Society for Reproductive Immunology. Jacksonville, Florida, Abstract #2
42. Aschkenazi, SO, Verwer, KMA, Foellmer, H. **Mor, G.** (2000) Differential effects of T-Helper-1 and T Helper-2 type cytokines on normal human trophoblast expression of Fas and Fas ligand: Possible role in implantation. American Society for Reproductive Immunology. Jacksonville, Florida, Abstract #25
43. Muñoz, A.A., Redlinger, R., Kohen, F., **Mor, G.** (2000) differential expression of estrogen receptors α and β in the thymus. American Society for Reproductive Immunology. Jacksonville, Florida, Abstract #27
44. **Gil Mor**, Joon Song, Wendi Brown, Frederick Naftolin Estrogen and the FAS/FAS Ligand System in Breast Cancer Cells: Functional Differences between Estradiol and Tamoxifen. Blue Ribbon presentation. SGI Chicago IL, Abstract # 8

45. Thomas Rutherford, Eva Sapi, Wendi Brown, Karlijn Verwer, Amanda Munoz, **Gil Mor** (2000) Fas and Fas Ligand Expression in Normal and Pathologic Ovarian Tissue. SGI Chicago IL, Abstract # 9

46. Wendi Brown, **Gil Mor**, Thomas Rutherford, Karrie Tartaro, Eva Sapi (2000) Fas Ligand Expression Is Regulated by Estrogens in Normal and Neoplastic Ovarian Epithelia. SGI Chicago IL, Abstract # 41

47. Joon Song, Eva Sapi, Jon Nilsen, Hyun C Lim, Frederick Naftolin, **Gil Mor** (2000) The Role of the Fas/Fas Ligand System in Breast Tissue: Normal Differentiation Versus Breast Cancer. . SGI Chicago IL, Abstract # 531

48. M Sbracia, R Poverini, A Rossi, M DeFelici, F Scarpellini, C Aragona, G Micara, **G Mor**. (2000) FAS-Receptor/FAS-Ligand System Regulates with an Autocrine/Paracrine Mechanisms the Apoptosis in Human Pre-Embryos. SGI Chicago IL, Abstract # 605

49. Brown, WD., Sapi, E., Verwer, KMA., **Mor, G.** (1999) Fas Ligand regulation in an ovarian organ culture system: Implications for ovarian cancer. American Society for Reproductive Immunology. Cooperstown, NJ ; Abstract # P-9

50. Verwer, KMA., Brown, WD., Foellmer, HG., **Mor, G.** (1999) Macrophage derived growth factors modulate Fas Ligand expression in cultured trophoblast cells: A role in implantation. American Society for Reproductive Immunology. Cooperstown, NJ ; Abstract # P-10

51. **Mor, G.**, Brown S., Rosen, R., Song, J., Brown WB., Naftolin, F. (1999) Regulation of Fas Ligand expression in breast cancer cells by estrogen: Functional differences between estradiol and tamoxifen. American Society for Reproductive Immunology. Cooperstown, NJ ; Abstract # O-9

52. Zaltsman, Y., **Mor, G.**, Ben-Hur, H., Gayer, N., Nevo, N., Kohen, F. (1999) Hormonal Regulation of Fas Ligand in the rat prostate: Implications for prostate cancer. Endocrine Society San Diego CA.

53. Nilsen, J., **Mor, G.**, Naftolin, F. (1999) Raloxifene is an estrogen agonist, inducing neurite outgrowth in PC12 cells. Society for Gynecologic Investigation, Atlanta, Georgia. Abstract # 723

54. Garcia-Velasco, J., Arici, A., Naftolin, F., Zreik, T., **Mor, G.** (1999) Macrophage-Derived growth factors modulate Fas ligand expression in endometrial stromal cells: a role in endoemtriosis. Society for Gynecologic Investigation, Atlanta, Georgia. Abstract #

55. Hsu, CD., Gutierrez, LS., Meaddough, E., Basheera, H., Lu, LC., Copel, JA., Harirah, H., **Mor, G.** (1999). Expression of Fas ligand by preeclamptic placenta. Society for Maternal-Fetal Medicine. San Francisco. Abstract #
56. **Mor, G**, Gutierrez L.S,, Eliza M., Kahyaogili, F., Arici, A. (1998). Induction of apoptosis mediated by the Fas-fas ligand system in human placental trophoblast and gestational trophoblastic disease. Society for Gynecologic Investigation. 45 th Annual Meeting. Atlanta, Georgia. Abstract # 55.
57. Senturk, L.M., **Mor, G.**, Gutierrez, L.M., Zeyneloglu, H.B., Bahtiyar, M.O., Arici, A. (1997). Monocyte Chemoattractant Protein-1 expression in human corpus luteum. American Society for Reproductive Medicine. 53Rd Annual Meeting. Cincinnati, Ohio.
58. Diano, S., **Mor, G.,** Horvath, T., Register, T., Adams, M., Naftolin, F. (1997). Estrogen formation by coronary arteries? .The presence of immunoreactive-Aromatase (irARO) and estrogen receptors (irER) in monkey and human coronary arteries. 8th Annual Meeting , NAM, Boston, MA.
59. Ben-Hur, H., **Mor, G.**, Blickstein, I., Likhman, I., Amir-Zaltsman, Y., Sharp, A., Insler, V., Globerson, A., & Kohen, F. (1993). Expression of estrogen receptors [ER] in human monocytes in relation to menopause and hormone replacement therapy. In: 23rd Annual Meeting of the Israel Immunological Society, #43. Ben-Gurion University, Ber-Sheba, Israel.
60. **Mor, G.**, Amir-Zaltsman, Y., Ben-Hur, H., Sharp, A., & Kohen, F. (1993). Expression of Estrogen receptors in Human Peripheral mononuclear cells is associated mainly with monocytes. In: 23rd Annual Meeting of the Israel Immunological Society, #54 . Ben-Gurion University, Ber-Sheba, Israel.
61. **Mor, G.**, Amir-ZAltsman, Y., Bernard, G., & Kohen, F. (1993). Evidence for the presence of estrogen receptors in monocytes. In: 75th Annual Meeting of the Endocrine Society. Las Vegas, Nevada.
62. Ben-Hur, H., **Mor, G.**, Blickstein, I., Dagani, R., Insler, V., & Kohen, F. (1991-1992). Immunofluorescence studies of estrogen and progesterone receptor distribiution in the human endometrium using anti-idiotypic antibodies . In: Annual Meeting of the Israel Endocrine Society. Jerusalem, Israel.

63. **Mor, G.**, Kukulansky, T., Kohen, F., & Globerson, A. (1991). Patterns of estrogen Receptor expression on thymocytesfrom young and old mice. In: Israel Immunological Society , 21st Annual Meeting. Rehovot, Israel.
64. Amir-Zaltsman, Y., **Mor, G.**, Barnard, G., Gayer, B., Lichter, S., & Kohen, F. (1991). Anti-idiotypic antibodies against anti-estradiol: Preliminary characterization and probes for the study of the estrogen receptor. In: Endocrine Society, Annual Meeting . Washington.
65. Amir-Zaltsman, Y., Levi, L., **Mor, G.**, Ben-Aroya, N., Koch, Y., & Kohen, F. (1990-1991). Anti-idiotypic antibodies against anti-buserelin: Probes for the study of the GnRH receptor. In: Annual Meeting of the Israel Endocrine Society. Tel-Aviv, Israel.
66. **Mor, G.**, Fajer, A., Barnard, B., Gayer, B., Lichter, S., & Kohen, F. (1990-1991). Monoclonal anti-idiotypic antibodies against anti-estradiol: use in the direct localization of estrogen receptor. In: Annual Meeting of the Israel Endocrine Society. Tel-Aviv, Israel.
67. **Mor, G.**, Fajer, A., Barnard, G., & Kohen, F. (1990). Use of fluorescent labeled monoclonal anti-idiotypic steroidal antibodies in the direct localization of cytoplasmatic and nuclear estrogen receptor. In: The Endocrine Society ,72 Annual Meeting. Atlanta, Georgia.
68. Fajer, A., Barnard, G., **Mor, G.**, & Kohen, F. (1989). Use of anti-idiotypic antibodies in the localization by immunofluorescence of parenterally administered monoclonal antibodies to estradiol in female rars. In: The Endocrine Society 71st Annual Meeting. Washington.
69. **Mor, G.**, Amir-ZAltsman, Y., Bernard, G., Gayer, B., Lichter, S., Osher, S., & Kohen, F. (1992). Characterization of an anti-idiotypic antibody that recognizes estrogen receptors. In: 74th Annual Meeting of the Endocrine Society, (pp. #731). San Antonio,Texas.
70. **Mor, G.**, Saphier, D., & Feldman, S. (1985). Effects of corticosterone (CS) upon paraventricular nucleus (PVN) multi-unit activity (MUA) following neurogenic stimulation. In: Annual Meeting of the Israel Endocrine Society, Abstr. # 76. Tel Aviv, Israel.
71. Naftolin, F., **Mor, G.**, Luquin, S., Fager, A., Lewis, C., Feefe, D., Kohen, F., & Garcia-Segura, L. (1993). Synaptic Plasticity in the hypothalamus arcuate nucleus during the estrus cycle is induced by estrogen and limited to the periventricular zone of reaction. In: 74th Annual Meeting of the Endocrine Society, #1804 . Las Vegas, Nevada.
72. Saphier, D., Abramsky, O., **Mor, G.**, & Ovadia, H. (1986). A physiological correlate of an immune response. In: 6th International Congress of Immunology. Toronto, Canada.

73. Saphier, D., **Mor, G.**, & Feldman, S. (1986). Effects of corticosterone on paraventricular nucleus multiple unit activity responses to neural stimuli in concious animals. In: 30th International Congress of Physiological Sciences. Vancouver, Canada.

LECTURES:

Lectures:

Outside Yale
(Main lectures since 1999-2007)

2007 Invited Speaker: 23th Annual Meeting of the Japanese Society for Immunology of Reproduction: Inflammation and pregnancy: The role of TLRs. Tokyo Japan

2007 Invited Speaker:New York Obstetrical Society Meeting: Biomarkers for the early detection of ovarian cancer. New York, NY

2007 Invited Speaker: xSamples Technology. Biomarkers development for cancer. Boston MA

2007 Invited Speaker: Human Reproduction in 2007. Early detection of ovarian cancer. Mykonos, Greece

2007 Invited Speaker: Human Reproduction in 2007. TLRs and pregnancy. Mykonos, Greece

2007 Invited Speaker: Menopause Society. New therapeutic approaches for the treatment of ovarian cancer. September Mar del Plata, Argentina

2007 Invited Speaker: Meeting of the International Society for Reproductive Immunology. Trophoblast immune interactions. Opatja, Croatia

2007 Invited Speaker: International Meeting on Women Health: Biomarkers for Ovarian Cancer. Valencia Spain,

2007 Invited Speaker: Early Detection Research Network, NCI: Blood Biomarkers for Cancer. Denver, CO

Invited Speaker: V International Meeting of Obstetrics and Gynecology: Immunology of Pregnancy. Valparaiso Chile

2007 Invited Speaker: V International Meeting of Obstetrics and Gynecology: Inflammation and Cancer. Valparaiso Chile

2007 Invited Speaker: V International Meeting of Obstetrics and Gynecology: Early Detection of Ovarian cancer. Valparaiso Chile

2007 Invited Speaker: Annual Meeting of the American Society for Reproductive Immunology: TLRs and Pregnancy. Toronto Canada

2007 Invited Speaker: V International Meeting of Obstetrics and Gynecology: Immunology of Pregnancy. Valparaiso Chile May 2007

2006 Invited Speaker: 13th Postgraduate Course "Recent Advances in Perinatal Medicine" Erice Italy

2006 Invited Speaker: Oncology Group: Advantages for early detection of Ovarian cancer. Tel Aviv Israel

2006 Invited Speaker: National Congress of Obstetrics and Gynecology. New Markers for Early detection of ovarian cancer. Ramat Gan Israel

2006 Invited Speaker: School of Medicine. Symposium on Immunology of pregnancy. Inflammation and pregnancy: the role of Toll Like Receptors. West Virginia University

2006 Invited Speaker: Annual Meeting, Sociedad Argentina de Endocrinologia Ginecologica y Reproductiva: Inflammation and Cancer. Buenos Aires Argentina

2006 Invited Speaker: Annual Meeting, Sociedad Argentina de Endocrinologia Ginecologica y Reproductiva: Biomarkers for early detection of Ovarian Cancer. Buenos Aires Argentina

2006 Invited Speaker: Annual Meeting, Sociedad Argentina de Endocrinologia Ginecologica y Reproductiva: Trophoblast-Immune interactions. Buenos Aires Argentina

I2006 Invited Speaker: Annual Meeting, Sociedad Argentina de Endocrinologia Ginecologica y Reproductiva: Trophoblast apoptosis. Buenos Aires Argentina

2006 Invited Speaker: Array BioPharma's. Inflammation and Cancer. Denver, Colorado

2006 Invited Speaker: Apoptosis and Cancer Wilkes-Barre University

2005 Invited Speaker: International Meeting of Gynecology. Early Detection and Ovarian Cancer. Medellin Colombia

2005 Invited Speaker: International Meeting of Gynecology. Immunology of Implantation. Medellin Colombia

2005 Invited Speaker: International Meeting of Gynecology. Cancer Progression and Inflammation. Medellin Colombia

2005 Invited Speaker: Inflammation and Cancer. Vaccination, Infection & Autoimmunity: Myth & Reality-VIAMR. Lausanne, Switzerland

2005 Invited Speaker: Early detection in Cancer. 11th World Congress of Menopause Buenos Aires Argentina,

2005 Invited Speaker: Inflammation and Ovarian Cancer progression. 11th World Congress of Menopause Buenos Aires Argentina,

2005 Invited Speaker: Isoflavones and the treatment of ovarian cancer. 11th World Congress of Menopause Buenos Aires Argentina,

2005 Invited Speaker: New markers for the early detection of ovarian cancer. EDRN Sterling Meeting Seattle Washington

2005 Invited Speaker: Apoptosis and Cancer: Annual Meeting of the Gynecologic Society Guayaquil Ecuador,

2005 Invited Speaker: Apoptosis and tissue remodeling Annual Meeting of the Gynecologic Society Guayaquil Ecuador,

2005 Invited Speaker: Phenoxodiol a new approach for the treatment of ovarian cancer. VI Congress of Menopause Bucaramanga Colombia

2005 Invited Speaker: The regulation of apoptosis in tissue remodeling and cancer. VI Congress of Menopause Bucaramanga Colombia.

2005 Invited Speaker: New Concepts in Reproductive Immunology. Department of Physiology Dartmouth University Hanover NH

2005 Invited Speaker: The immunology of the female reproductive tract. Annual Meeting Society of Mucosal Immunity Boston MA

2005 Invited Speaker: Immunology of Implantation. Humboldt University Berlin Germany

2005 Invited Speaker: Toll Like Receptors and implantation. Perinatal Research Brank, NICHD, NIH. Detroit MI

2004 Invited Speaker: Apoptosis and Cancer: Detection and Treatment: MOFFITT Cancer Center Tampa Florida.

2004 Invited Speaker: Sex Hormones and the Immune System. 2nd World Congress on Women Mental Health. Washington DC

2004 Invited Speaker: The Innate Immune System: trophoblast survival and apoptosis. IX International Congress of Reproductive Immunology Hakone, Japan

2004 Invited Speaker: Menopause, Sex Hormones and the Immune System: Curso de postgrado en Climaterio. Buenos Aires Argentina

2004 Invited Speaker: The immune system and Reproduction. IVIG: Reproductive Immunology San Francisco CA

2004 Invited Speaker: Apoptosis and Cancer. Nevada Cancer Institute.

2004 Invited Speaker. Sex Hormones and the Immune System. International al Meeting of Menopause. Lima Peru

2004 Invited Speaker: Apoptosis Ovaric: International al Meeting of Menopause. Lima Peru

2003 Invited Speaker: Apoptosis and cancer: Weizmann Institute of Science Rehovot Israel

2003 Invited Speaker: Sex hormones as Survival factors. Jornadas Nacionales de Climaterio. Salta, Argentina

2003 Invited Speaker: Sex Hormones and the Immune System. Jornadas Nacionales de Climaterio. Salta, Argentina

2003 Invited Speaker: Apoptosis and the Ovary. Jornadas Nacionales de Climaterio. Salta, Argentina .

2003 Invited Speaker: Apoptosis and Cancer. Northwestern University, Chicago

2003 Invited Speaker: Immunology of Implantation. Northwestern University, Chicago

2003 Invited Speaker: XII World Congress of Gestational Trophoblastic Disease. Sheraton Boston Hotel. Boston MA

2003 Invited Speaker: Monocytes and implantation. PRB, NIH.

2002 Invited Speaker: Life after death? Survival by apoptosis in reproductive tissues. DOD Breast cancer Training Program- Fox Chase Cancer Center, Philadelphia 2002

2002 Invited Speaker: Sex hormones and the Immune system. 3rd Annual conference on Sex and Gene Expression. The Hayes Mansion Conference Center-San Jose California

2001 Invited Speaker: Estrogen, macrophages and the Fas/FasL system: Understanding the Biology of Sex Differences, Scientific Advisory Meeting:: Sex Differences in Immunology and Autoimmunity. Boston MA

2001 Invited Speaker: Apoptosis and Cancer. International Menopause Day, Santiago-Chile

2001 Invited Speaker: Sex Hormones and the Immune System: Cancer and Autoimmunity. International Menopause Day, Santiago-Chile

2001 Invited Speaker: Sex hormones and the immune system: implications for menopause and autoimmunity. 4th International Symposium Women's Health and Menopause Washington DC

2001 Invited Speaker: Autoimmune diseases and Hormone Replacement Therapy. Menopause Society Asuncion Paraguay

2001 Invited Speaker: Estrogen receptors α and β in reproductive tissues. Menopause Society Asuncion Paraguay

2001 Invited Speaker: Immunology of Gynecologic Cancers. Menopause Society Asuncion Paraguay

2001 Invited Speaker: The Fas/FasL system in reproductive Tissues: Normal Development and Autoimmunity Annual Meeting of the American Society of Reproductive Immunology. Santiago, Chicago

2001 Invited Speaker: Apoptosis and Cancer. Brown University Grand Rounds. Providence RI

2001 Invited Speaker: Immunology of implantation. Perinatology Research Branch Intramural Division, NICHD. Detroit

1999 Invited Speaker: Immune Disorders in Menopausal Women. The North American Menopause Society. New York

2000 Invited Speaker: Autoimmune diseases and Hormone Replacement Therapy. Menopause Society Santiago de Chile

2000 Invited Speaker: Estrogen receptors α and β in reproductive tissues. Menopause Society Santiago de Chile

2000 Invited Speaker: Immunology of Gynecologic Cancers. Menopause Society Santiago de Chile

2000 Invited Speaker: Sex Hormones and the Immune System. XVII Jornadas de Obstetricia y Ginecologia. Buenos Aires Argentina.

2000 Invited Speaker: The effect of Hormone Replacement Therapy in Autoimmune Diseases. XVII Jornadas de Obstetricia y Ginecologia. Buenos Aires Argentina.

1999 Invited Speaker: Immunology of Gynecologic Cancers. XVII Jornadas de Obstetricia y Ginecologia. Buenos Aires Argentina.

1999 Invited Speaker: Fas/Fas Ligand system in tumor-immune cells interaction. Annual meeting of the American Society of Reproductive Immunology. New York

At Yale

- Grand Rounds Yale Cancer Center: Biomarkers for the early detection of ovarian cancer. June 2007
- Yale Cancer Center: Developmental and Therapeutics Research Program: TLRs, inflammation and Cancer. January 2006
- Yale Cancer Center: Ovarian Cancer Research Program: Serum Proteins Markers for Early Detection of ovarian cancer. March 2006
- Yale Cancer Center, Therapeutic Radiology Lectures: Inflammation and Cancer: 2006
- Grand Rounds Department of Obstetrics and Gynecology: Serum Protein Markers for early detection of Ovarian cancer. 2006
- Ovarian Cancer Research Program: Serum Protein Markers for early detection of ovarian cancer. 2005
- Pharmacology: Apoptosis and cancer 2004
- Immunobiology Seminar Series Lectures: A lethal talk: Fas-FasL in tumor Immune cells interaction. 1999
- OB/Gyn Residents Seminar: Immunology of Reproduction. 1999, 2000, 2001 and 2002
- Gynecologic Oncology Residents lecture: apoptosis and cancer. 2001
- Grand Rounds Yale Cancer Center: Life after death? Survival by apoptosis in reproductive tissues. 2002
- Grand Rounds Pathology : Apoptosis and Cancer 2003
- Grand Rounds Department of Obstetrics and Gynecology: Phenoxodiol a new approach for the treatment of ovarian cancer. 2002

Exhibit B

Second-Trimester Maternal Serum Placental Growth Factor and Vascular Endothelial Growth Factor for Predicting Severe, Early-Onset Preeclampsia

Bruno M. Polliotti, PhD, A. Gordon Fry, MD, Devereux N. Saller, Jr, MD, Robert A. Mooney, PhD, Christopher Cox, PhD, and Richard K. Miller, PhD

OBJECTIVE: To determine whether alterations in second-trimester maternal serum cytokine concentrations can identify women at risk for developing severe, early-onset preeclampsia.

METHODS: Patients with severe preeclampsia requiring delivery prior to 34 weeks ($n = 20$) were each matched by gestational age, gravidity, parity, and sample freezing time with three healthy controls who delivered at term ($n = 60$). By using second-trimester maternal sera originally collected for fetal aneuploidy screening, the concentrations of placental growth factor, vascular endothelial growth factor, granulocyte colony-stimulating factor, endothelin-1, and human chorionic gonadotropin were compared between patients and controls. Logistic regression analysis was used to estimate odds ratios for high versus low (median split) cytokine concentrations with respect to the development of severe, early-onset preeclampsia. Receiver operating characteristic (ROC) curves based on a second logistic regression, using actual cytokine values, were plotted to illustrate reciprocal impact on sensitivity and specificity.

RESULTS: Placental growth factor and vascular endothelial growth factor levels were significantly lower in patients than in controls. No significant differences were observed for the other cytokines. The odds ratios (with 95% confidence intervals) were 15.54 (3.29, 73.40) for vascular endothelial growth factor and 4.20 (1.35, 13.06) for placental growth factor. Receiver operating characteristic analysis of placental growth factor and vascular endothelial growth factor confirmed that both were useful in discriminating between patients and controls. Models combining both vascular endothelial growth factor and placental growth factor provided the best performance for identifying patients at risk for developing severe, early-onset preeclampsia, according to both odds ratios and ROC analyses.

CONCLUSION: Combined analysis of placental growth factor and vascular endothelial growth factor is potentially useful as a tool for early identification of patients at risk for developing severe, early-onset preeclampsia. (Obstet Gynecol 2003;101:1266–74. © 2003 by The American College of Obstetricians and Gynecologists.)

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Despite decades of research, the pathogenesis of preeclampsia remains poorly understood, and attempts to identify early markers of the disorder have been disappointing. Biochemical markers that could predict the subsequent onset of preeclampsia before maternal clinical manifestations become apparent would be advantageous because they may elucidate the pathophysiologic mechanisms of the disorder and identify specific patients early in pregnancy who are at high risk for developing preeclampsia.[1,2] Once identified, these women may benefit from targeted therapy that could prevent or diminish the effects of the disease. Because the preponderance of maternal and perinatal morbidity and mortality occurs when disease develops at an early gestational age,[3,4] early prediction of preeclampsia would have the greatest potential to favorably impact maternal and perinatal outcome if it can identify the subset of women destined to develop severe, early-onset disease.

The association between abnormal placentation and preeclampsia is well known and is thought to involve inadequate trophoblast invasion of maternal spiral arteries during early gestation.[5] Evidence of placental derangement may be reflected in maternal circulation by alterations in the concentration of biochemical markers involved in the process of normal placental development. Placental growth factor and vascular endothelial growth factor, members of the platelet-derived growth factor family, are both important local mediators of angiogenesis in the human placenta[6] and can be isolated from the maternal circulation. Changes in the circulating concentrations of these factors may represent abnormal

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placental development in pregnancies destined to develop preeclampsia. Recent publications present contradictory results for placental growth factor, showing decreased maternal serum levels early in the second trimester[7,8] or levels that are not significantly different from normal pregnancies at the same gestational age.[9] Livingston et al also have observed a decrease of placental growth factor at term[10] but not earlier in gestation.[9] The role of vascular endothelial growth factor is similarly unclear. Whereas some investigators report an increase in circulating maternal levels in patients with preeclampsia, as compared with patients with normal pregnancies,[11,12] others report a decrease.[10,13,14] However, most of these studies were performed after preeclampsia was clinically evident, and the pattern of circulating vascular endothelial growth factor levels earlier in pregnancy is not known.

Other cytokines have also been implicated in the etiology of preeclampsia. Granulocyte colony stimulating factor may play a role in the development of preeclampsia by acting as a stimulus for vascular endothelial damage through the activation of granulocytes, and circulating granulocyte colony stimulating factor levels are reported to be elevated in maternal circulation in preeclampsia.[15] Endothelin-1 is a potent vasoconstrictor, and increased circulating levels serve as a marker for endothelial damage. Endothelin-1 in the placenta also stimulates trophoblast cell proliferation and invasion in vitro, implying a potential role in pathogenesis of preeclampsia at the placental level.[16] Whereas circulating maternal levels of endothelin-1 appear to be elevated,[17] placental production of endothelin-1 seems to be reduced in preeclamptic pregnancies.[16] In addition, granulocyte colony stimulating factor is also reported to stimulate endothelin-1, and this interaction has been associated with preeclamptic mechanisms.[18]

Because increased maternal concentrations may be a marker for abnormal placentation in general, human chorionic gonadotropin (hCG) has also been studied as a potential tool for predicting the development of preeclampsia. Increased serum levels of β-hCG have been found during the second trimester in women who later developed preeclampsia.[19] Free α-hCG subunit levels have also been reported to be significantly higher among patients with severe preeclampsia.[20]

The current data relating to the role of these cytokines in preeclampsia are inconsistent, explained in part by differing methodologies and experimental designs among the studies. It is also possible that the examination of multiple cytokines might be superior to the analysis of a single one. We therefore designed a study of multiple cytokines that, by focusing on a specific, narrowly defined subset of preeclamptic patients, addresses some of the discrepancies observed in previous studies. The purpose of this investigation was to determine whether the circulating concentrations of a combination of selected cytokines (placental growth factor, vascular endothelial growth factor, granulocyte colony stimulating factor, endothelin-1, and hCG) in second-trimester maternal serum could be used to predict the subsequent development of preeclampsia. Because most maternal and fetal morbidity and mortality occurs when preeclampsia presents at early gestational ages, we confined our analysis to women who were delivered before 34 weeks' gestation because of severe preeclampsia.

MATERIALS AND METHODS

This was a case–control study comparing women who developed severe preeclampsia before 34 completed weeks' gestation and matched, healthy controls who delivered at term with respect to the concentration of cytokines that had been obtained in the second trimester. Maternal serum samples were originally collected for purposes of antenatal screening for fetal aneuploidy and neural tube defects. This screening program, which uses a triple marker assay of maternal serum for α-fetoprotein, estriol, and free β-hCG concentrations, is available to all pregnant women in the New York State Finger Lakes region through the Rochester Regional Genetics Program. Currently, approximately 60% of pregnant women in the Finger Lakes region elect to have second-trimester serum screening performed.

Candidates for inclusion in the study were identified through a computerized search of a perinatal database that included all deliveries occurring between January 1, 1999 and May 31, 2001 at Strong Memorial Hospital, University of Rochester Medical Center. The hospital records of study candidates were then carefully reviewed with regard to study criteria, described below. Stored serum samples of patients meeting these criteria were analyzed for cytokine concentration. The serum levels of placental growth factor, vascular endothelial growth factor, endothelin-1, and granulocyte colony stimulating factor were quantified with an enzyme-linked immunosorbent assay with a sensitivity of 7, 1, 1, and 20 pg/mL, a specificity nearly 100% (with various levels of cross-reactivity), a coefficient of variation interassay of 11.2, 7.3, 5.7, and 3.7% and a coefficient of variation intra-assay of 5.4, 5.4, 4.4, and 1.8%, respectively (R&D Systems Inc., Minneapolis, MN). A chemiluminescent enzyme immunoassay for hCG was used, with a sensitivity of 1 mIU/mL, a specificity of nearly 100% (with a cross-reactivity of 127% with hCG-β subunit), a coefficient of variation interassay of 6.5%, and a coefficient of variation intraassay of 3% (Immulite DPC, Los Angeles,

CA). This research study protocol was reviewed and approved by the Research Subjects Review Board at the University of Rochester.

The study was designed to evaluate preeclamptic women whose disease was severe enough to mandate delivery at an early gestational age for either maternal or fetal indications. To be considered for inclusion in the study, all candidates must have shown an unequivocal history of both the following: 1) severe preeclampsia warranting delivery based on maternal or fetal indications, and 2) delivery before 34 completed weeks of gestation. Categorization of disease in study subjects was defined in accordance with the most recent consensus recommendations for classifying hypertensive disorders in pregnancy.[21,22] Specifically, preeclampsia was defined as newly detected hypertension (systolic blood pressure [BP] greater than or equal to 140 mm Hg, or diastolic BP greater than or equal to 90 mm Hg) with proteinuria (greater than or equal to 300 mg total urinary protein over a 24-hour collection period), both developing after 20 weeks' gestation. *Severe preeclampsia* was defined as preeclampsia complicated by either 1) severe hypertension (systolic BP greater than or equal to 160 mm Hg or diastolic BP greater than or equal to 110 mm Hg, measured on at least two separate occasions 6 hours apart), or 2) at least 5 g total urinary protein within a 24-hour collection period. Preeclampsia was also classified as severe in the presence of specific and otherwise unexplained abnormal laboratory or physical findings, regardless of elevated blood pressure or proteinuria. These findings included 1) elevated levels of aspartate aminotransferase (greater than 72 IU/L), 2) thrombocytopenia (platelet count less than 100,000/mm^3), 3) pulmonary edema, 4) oliguria (less than 500 mL urine in 24 hours), and 5) abnormal neurologic findings (excluding headache occurring in an individual with a history of recurring or chronic headache).

Preeclamptic patients were also required to have clear indications for delivery based on the severity of their disease before being included as study subjects. Maternal indications for delivery included severe hypertension despite maximal doses of oral antihypertensive agents, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, new onset of neurologic symptoms, thrombocytopenia or abnormal liver function tests without other evidence of HELLP, oliguria, pulmonary edema, new-onset coagulopathy, and epigastric pain. Fetal indications included repetitive late decelerations, bradycardia, and a persistent biophysical score of 4 or less.

Individuals with chronic hypertension, diabetes mellitus, and preexisting renal disease were eligible for inclusion if severe preeclampsia was unequivocally diagnosed after 20 weeks, based on new development of abnormal laboratory or physical findings described previously. Individuals with multiple gestations and with growth-restricted fetuses were also eligible for inclusion. The presence of severe blood pressure elevation or proteinuria alone, in the absence of concurrent clinical or laboratory abnormalities, was not sufficient to allow the inclusion of individuals with preexisting chronic hypertension or renal disease. Patients who were delivered because of nonreassuring fetal status were included if other clinical criteria were met.

Patients were excluded if delivery occurred after 34 weeks (even when severe preeclampsia developed before 34 weeks) or if delivery occurred because of factors related to conditions other than severe preeclampsia (eg, preterm labor, preterm premature rupture of membranes, chorioamnionitis, or nonreassuring fetal status clearly unrelated to preeclampsia [eg, umbilical cord prolapse]). Patients with preexisting hypertension or proteinuria were not included unless the new onset of abnormal physical or laboratory findings defining severe preeclampsia developed.

Stored samples from three control subjects were identified for each patient with preeclampsia and matched with preeclamptic patients based on maternal age, gestational age, gravidity, parity, and length of time of serum sample storage.

Differences between means of the two subject groups for clinical variables and for cytokine concentrations were assessed with unequal Student t test with unequal variance. Because some of the variables were highly skewed, parity and gravidity in particular, we also used a nonparametric test (Kruskal-Wallis test). A P value of less than .05 was considered to be significant. For cytokines found to have significantly different second-trimester concentrations between patients and controls, logistic regression analysis was used to model the probability of developing severe, early-onset preeclampsia. Two separate logistic regressions were performed. For the first analysis, the cytokine values were divided at the median and scored as low (below the median) or high (above the median). Odds ratios from this analysis are reported, together with 95% confidence intervals. The second analysis used the actual cytokine concentrations as predictor variables; this analysis was used to develop a receiver operating characteristic (ROC) curve for the combined set of cytokines. These analyses were performed by fitting linear logistic regression models for binary data by using the method of maximum likelihood. The maximum likelihood estimation was carried out with the Fisher scoring algorithm.[23]

Table 1. Clinical Characteristics of Preeclamptic Patients

Maternal characteristics	Number of patients (n = 20)
Hypertension	19
Proteinuria	19
Preexisting chronic hypertension	8
Preexisting renal disease	1
Preexisting diabetes	1
Placental abruption	1
Multiple gestation	1 (twins)
Indication for delivery	
Maternal	18
Fetal	2
Complications mandating delivery	
HELLP syndrome	8
Abnormal LFT (without HELLP)	6
Thrombocytopenia (without HELLP)	0
Pulmonary edema	3
Oliguria	3
Neurologic changes	2
Fetal biophysical profile ≤ 4/10	2

HELLP = hemolysis, elevated liver enzymes, low platelets; LFT = liver function tests.

Three patients had more than one complication mandating delivery. Therefore, the total number of complications listed is greater than the total number of cases of preeclampsia.

RESULTS

Between January 1, 1999 and May 31, 2001, 129 patients were delivered preterm with severe preeclampsia at Strong Memorial Hospital. Of these, 20 patients fulfilling the clinical inclusion criteria for both diagnoses of severe preeclampsia and delivery before 34 weeks with a stored second-trimester serum sample suitable for cytokine analysis were identified. The clinical characteristics of these 20 women are summarized in Table 1, along with the indications for delivery. One patient had neither hypertension nor proteinuria. This individual was delivered after she developed HELLP syndrome. She also represented the only individual with a multiple gestation (twin pregnancy). Hemolysis, elevated liver enzymes, low platelets syndrome was the single most common indication for delivery, and the majority of patients were delivered for maternal rather than fetal indications. No patients developed a coagulopathy or epigastric pain.

The 20 cases of preeclampsia were compared with 60 normal control patients (three per patient with preeclampsia). Comparison of the clinical characteristics of the two groups is summarized in Table 2. Maternal age, gravidity, parity, and gestational age refer to data at the time of sampling in the second trimester. Blood pressure, proteinuria, gestational age, and birth weight refer to data collected at or near the time of delivery. Blood pressure values are the mean of the first two readings that were separated by at least 6 hours, taken during the hospital admission in which delivery occurred. Some control subjects did not have blood pressure data recorded in such manner. In these instances, the last recorded blood pressure value, either before or after admission for delivery, was used. For preeclamptic patients, proteinuria was assessed during the hospital admission in which delivery occurred. For control subjects, the last recorded assessment of urine protein before delivery, either before or after admission for delivery, was used. Three preeclamptic patients did not have a complete 24-hour urine collection performed. For these patients, proteinuria was defined in accordance with consensus recommendations[22] as greater than or equal to a 1+ reading on qualitative dipstick analysis (corresponding to approximately 0.3 g/L), obtained in at least two random urine specimens. One preeclamptic patient did not have proteinuria. The two groups were perfectly matched for maternal age, gravidity and parity, and the gestational age at time of the sampling. The mean gestational age at the time of delivery was 30.7 weeks for patients with preeclampsia and 38.2 weeks for control subjects. As expected, blood pressure values were significantly higher in the preeclamptic patients as compared with the control subjects. No control subjects had proteinuria. Six cases of preeclampsia were also associated with intrauterine growth restriction, compared with none in the control group. No patients with diabetes or chorioamnionitis were found in either group.

Table 2. Characteristics of the Study Groups

	Preeclampsia patients	Matched controls	Significance
Maternal age (y)	25.7 ± 4.9	27.2 ± 4.9	$P = .27$
Gestational age at time of sampling (wk)	17.0 ± 1.8	16.9 ± 1.5	$P = .93$
Gravidity	2.4 ± 1.6	2.1 ± 1.2	$P = .48$
Parity	0.7 ± 0.9	0.7 ± 0.9	$P = .84$
Systolic blood pressure	160 ± 17	113 ± 9	$P < .005$
Diastolic blood pressure	96 ± 13	66 ± 5	$P < .005$
Birth weight (g)	1345 ± 512	3407 ± 461	$P < .005$

Data are presented as mean ± standard deviation.

Significance for P value < 0.05, using unequal Student t test and Kruskal-Wallis test.

Table 3. Cytokine and Growth Factor Concentrations in Preeclamptic Patients and Matched Control Subjects

	Preeclampsia patients	Matched controls	Statistical significance
PlGF (pg/mL)	61.3 ± 28.1	122.4 ± 81.0	$P < .001$
VEGF (pg/mL)	2.57 ± 1.45	6.03 ± 4.64	$P < .001$
ET-1 (pg/mL)	2.07 ± 0.97	1.92 ± 0.63	$P = .54$
GCSF (pg/mL)	94.8 ± 50.8	85.4 ± 36.1	$P = .44$
hCG (IU/mL)	39.5 ± 22.1	37.1 ± 16.5	$P = .71$

PlGF = placental growth factor; VEGF = vascular endothelial growth factor; ET-1 = endothelin-1; GCSF = granulocyte colony stimulating factor; hCG = human chorionic gonadotropin.

Significance for P value < .05, using unequal Student t test and Kruskal-Wallis test.

Maternal serum concentrations of placental growth factor and vascular endothelial growth factor were significantly reduced in cases of preeclampsia (Table 3). No significant differences in the concentrations of endothelin-1, granulocyte colony stimulating factor, and hCG were observed between the two groups. The raw data, including individual factor concentrations and gestational age at the time each sample was obtained, are shown for maternal serum placental growth factor (Figure 1, top) and vascular endothelial growth factor (Figure 1, bottom) levels. Both growth factors were decreased by 40–50% compared with the controls.

To estimate odds ratios, logistic regression analysis was used to model the probability of developing severe preeclampsia based on second-trimester placental growth factor and vascular endothelial growth factor concentrations. Growth factor concentrations were dichotomized such that an individual value was considered either *normal* or *decreased*, based on whether it was above or below the respective median value of the sample distribution (80.8 pg/mL for placental growth factor, 4.20 pg/mL for vascular endothelial growth factor). Odds ratios were estimated by developing models based on the concentrations of placental growth factor and vascular endothelial growth factor alone, as well as a third model incorporating values of both factors (Table 4). The resulting odds ratios clearly demonstrate that, when considered individually, reduced levels of either placental growth factor or vascular endothelial growth factor are associated with an increased probability of developing severe, early-onset preeclampsia. However, when data from both factors are incorporated into a single model, the probability of developing severe, early-onset preeclampsia based on decreased second-trimester levels is even greater.

Receiver operating characteristic analyses of placental growth factor and vascular endothelial growth factor as individual markers demonstrated convincing evidence for the use of these markers in identifying women at risk for developing severe, early-onset preeclampsia with areas under the curve equal to 0.799 and 0.773 for placental growth factor and vascular endothelial growth factor, respectively (Figure 2). Receiver operating characteristic curves based on a second logistic regression, using actual cytokine values, were plotted to illustrate the sensitivity–specificity trade off. Receiver operating characteristic curve analysis for the *combination* of placental growth factor and vascular endothelial growth factor present even greater value as a predictive method with an area under the curve equal to 0.923. The combination of endothelin-1 and granulocyte colony stimulating factor to placental growth factor and vascular endothelial growth factor did not significantly increase the area under the curve value (0.928).

DISCUSSION

We determined that second-trimester serum levels of vascular endothelial growth factor and placental growth factor were significantly decreased when compared with normal control subjects at similar gestational ages. These results demonstrate that analysis of circulating vascular endothelial growth factor and placental growth factor levels appears to be a useful tool for the early identification of pregnant women at increased risk for developing severe, early-onset preeclampsia. Although both vascular endothelial growth factor and placental growth factor performed well individually, the logistic regression models and ROC analyses suggest that these factors perform better when both vascular endothelial growth factor and placental growth factor levels are combined as a single model than either does alone. The addition of granulocyte colony stimulating factor, endothelin-1, and hCG to the combined placental growth factor/vascular endothelial growth factor model did not improve the ability to identify these patients.

Because both may influence vascular development of the placental bed and regulate villus development and invasion, vascular endothelial growth factor and placental growth factor are attractive candidates for involvement in the etiology of preeclampsia. Because the placenta is reduced in its degree of invasion and size and is a major site of production for vascular endothelial growth factor and placental growth factor, we speculate

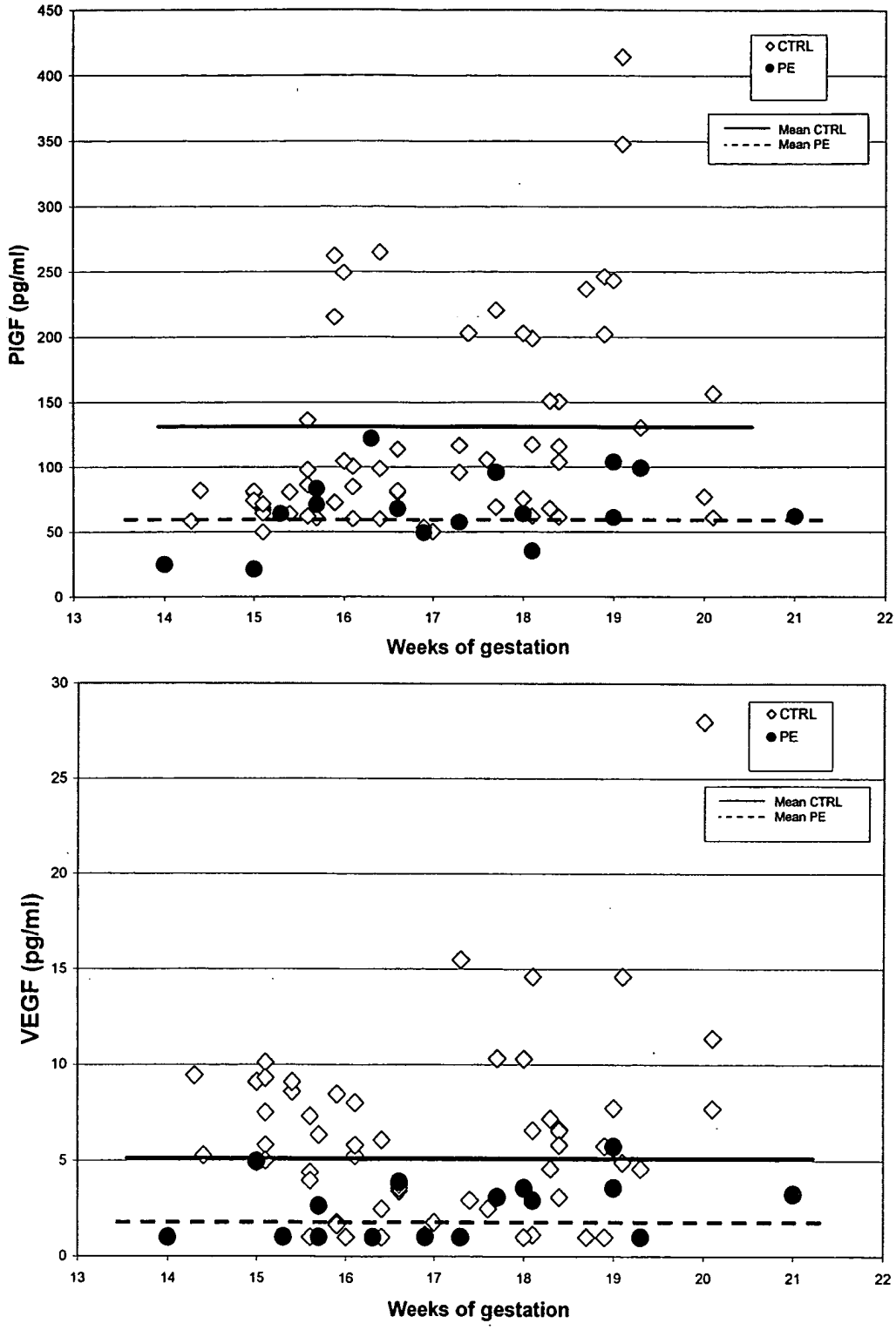

Figure 1. Maternal serum concentrations of placental growth factor *(top)* and vascular endothelial growth factor *(bottom)* collected between 14 and 21 weeks' gestation. *Black circles* = preeclamptic (PE) patients; *white squares* = matched control subjects (CRTL); *solid line* = mean value of the controls; *dashed line* = mean value of preeclamptic patients.
Polliotti. Severe Early-Onset Preeclampsia. Obstet Gynecol 2003.

Table 4. Odds Ratios Associated With Developing Severe, Early-onset Preeclampsia Based on Decreased Second-Trimester Levels of PIGF and VEGF Using Different Logistic Regression Models

Model	PIGF	VEGF
PIGF and VEGF	7.77 (2.02, 29.89)	24.77 (4.63, 132.47)
PIGF	4.20 (1.35, 13.06)	
VEGF		15.54 (3.29, 73.40)

Abbreviations as in Table 3.

Values in parentheses represent limits of the 95% confidence interval. Logistic regression models were dichotomized at the median value for each factor concentration.

that reduced maternal levels of vascular endothelial growth factor and placental growth factor reflect the impaired production of these factors by the placentae in women with severe preeclampsia.

Although second-trimester maternal serum vascular endothelial growth factor levels in preeclamptic pregnancies have not been examined as extensively, placental growth factor levels have received considerable attention recently.[7-9,24,25] The discrepant results of these studies make it difficult to clearly appreciate the role of these maternal and placental factors in the etiology of preeclampsia. A recent editorial published while our investigation was underway outlined potential areas of concern in studies of this type.[2] The methods employed in our study have addressed many factors that contribute to discrepant results. For example, our serum samples were preserved at a constant temperature of −20C, in a single freezer, and never left the storage facility at Strong Memorial Hospital. None of the specimens were thawed and refrozen before their use for this study. These specimens were carefully matched for the freezing time between preeclampsia patients and controls (three for each case of preeclampsia). Our cytokine assays were used in previous studies (R&D Systems Inc.). However, potential sources of discrepancy remain in our study. Although several vascular endothelial growth factor isoforms exist (vascular endothelial growth factor$_{121, 165, 189, 206}$ AA residues), our assay was designed to detect only vascular endothelial growth factor$_{165}$, and our results should be compared only with results that detect a similar isoform. This observation could also be generalized to placental growth factor, although its diversity seems confined to only two isoforms. The Quantikine immunoassay that we used for this study is designed to specifically measure the placental growth factor-1 isoform. However, the manufacturer (R&D Systems Inc.) reports up to 50% cross-reactivity with recombinant placental growth factor-2 isoform and 5% cross-reactivity with a recombinant placental growth factor heterodimer. Clearly, the potential effect of possible differential expression of various isoforms of these growth factors in preeclampsia is an area that requires further study. Finally, because we analyzed serum rather than plasma, the concentrations of some factors may

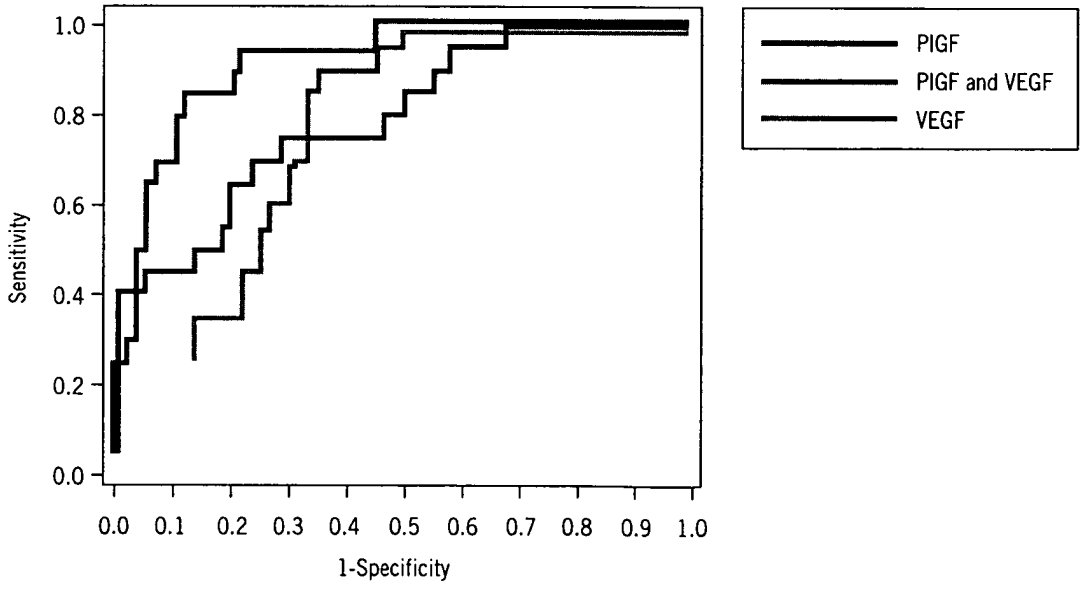

Figure 2. Receiver operating characteristic curves for assays of maternal serum for placental growth factor (PIGF), vascular endothelial growth factor (VEGF), and PIGF/VEGF combined. The area under the curve, respectively 0.799, 0.773, and 0.923, demonstrates the ability of cytokine analysis to differentiate preeclampsia from normal pregnancies, with the value 1.0 representing 100% sensitivity and specificity, and the value 0.50 having no discriminatory power.

Polliotti. Severe Early-Onset Preeclampsia. Obstet Gynecol 2003.

have been spuriously elevated because some of these substances are released from platelets when blood coagulates.

Experimental results from various studies of this design are also subject to inconsistent results based on whether preeclampsia is mild versus severe, occurs at term versus preterm, is complicated by maternal medical conditions, or involves abnormalities of fetal growth. Investigators from different studies may in fact be comparing "different diseases," thus arriving at different results. Given that early-onset preeclampsia and preeclampsia at term have distinctly different clinical implications, they may also have distinctly different pathophysiologic mechanisms. For this reason, we sought to carefully define the subtype of preeclampsia to be studied and restrict our study to the subtype responsible for the largest proportion of morbidity and mortality. Most other published studies have not restricted analysis of preeclamptic patients to those with severe disease, although the study by Tidwell et al[8] is a notable exception. This group found no difference in second-trimester placental growth factor concentrations in women who ultimately developed severe preeclampsia. However, in contrast to our investigation, the mean gestational age at delivery in that study was at term (38.3 weeks).

We also did not exclude women with preexisting risk factors for developing preeclampsia (maternal hypertension, renal disease, diabetes, etc), which is commonly done in investigations of similar design. One reason for excluding these patients was to eliminate potential confounding variables in the diagnosis of preeclampsia when such high-risk factors are present. To address this concern, we relied on strict, widely accepted clinical diagnostic criteria and indications for delivery,[21,22] to ensure that only patients delivered because of severe preeclampsia, rather than other complications relating to these preexisting medical conditions, were included. Furthermore, women already at increased risk for developing severe preeclampsia because of certain medical complications are precisely those who may benefit the most, in terms of additional counseling and possible intervention, by further defining their risk early in pregnancy.

Finally, because abnormal placentation can also affect fetal growth, the presence of intrauterine growth restriction was a major concern in this study. A recent study published while our investigation was underway found decreased levels of maternal placental growth factor during first trimester in pregnancies complicated by intrauterine growth restriction, but not in those destined to develop preeclampsia.[25] This suggests that the relationship of growth factors levels with preeclampsia may be confounded by the presence of a growth-restricted fetus. In our data set, only six cases of preeclampsia were accompanied by intrauterine growth restriction, and these revealed no significant differences in maternal growth factor levels when compared with other cases of preeclampsia without intrauterine growth restriction. Nonetheless, the sample size of our study does not permit us to fully assess the possible relationship between vascular endothelial growth factor and placental growth factor levels patterns and the coexistence of intrauterine growth restriction with preeclampsia.

In conclusion, this case–control study demonstrates that a combined analysis of second-trimester maternal placental growth factor and vascular endothelial growth factor levels is a potentially useful tool for identifying women at increased risk for the development of severe, early-onset preeclampsia. However, this preliminary study must be confirmed by a prospective study to assess the importance of the disease severity in the process of diagnosis and to allow separation of cause from effect. Mild preeclampsia and preeclampsia occurring at later gestational ages could respond differently or less specifically and warrant further investigation.

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